PATIENT LEAFLET IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) – 1986

The medicine is dispensed with a doctor's prescription only

Prograf® capsules

Prograf® 0.5 mg capsules **Prograf® 1 mg capsules** **Prograf® 5 mg capsules**

Composition

Each capsule contains:

Tacrolimus 0.5 mg Tacrolimus 1 mg Tacrolimus 5 mg

For information regarding inactive ingredients and allergens, see section 2 - "Important information about some ingredients of the medicine" and section 6 - "Additional information".

Read the entire leaflet carefully before using the medicine. This leaflet contains concise information about the medicine. If you have additional questions, refer to the doctor or the pharmacist.

This medicine has been prescribed for your treatment. Do not pass it on to others. It may harm them even if it seems to you that their medical condition is similar.

1. What is the medicine intended for?

Prophylaxis of transplant rejection in liver, kidney or heart allograft recipients.

Treatment of allograft rejection resistant to treatment with other immunosuppressive drugs.

Prograf belongs to a group of medicines that suppress the immune system. Following organ transplant (such as liver, kidney and heart) your body's immune system will try to reject the new organ. Prograf is used for modulation of your body's immune reaction and allows your body to accept the transplanted organ.

Therapeutic class: immunosuppressive agents.

2. Before using the medicine

Do not replace with another tacrolimus preparation, unless the doctor from the transplant clinic you are treated in approves that.

Do not use this medicine if:

- You are sensitive (allergic) to tacrolimus or to any of the other ingredients this medicine contains (see section 6 – "Additional information").
- You are sensitive (allergic) to any antibiotic of the macrolide group (e.g. erythromycin, clarithromycin, josamycin).

Special warnings regarding the use of the medicine

FOR YOUR ATTENTION, it is important to ascertain that you always receive the same medicine prescribed by your transplant specialist each time you get the medicine at the pharmacy. In the event you find out that the medicine you received looks different from the one you usually receive, or the directions for use have been changed, immediately refer to the pharmacist in order to confirm that you have been supplied with the correct medicine. Any replacement or change in dosing of a medicine containing tacrolimus (the active ingredient in the medicine) must be performed under the knowledge and approval of the physician from the transplant clinic you are being treated in. Please check the commercial name of the medicine written by the physician in the prescription vis-à-vis the medicine you have received from the pharmacist and verify that the names are identical.

Inform your doctor before using Prograf:

- You need to take Prograf every day, so long as you need immunosuppression in order to prevent your transplanted organ from being rejected. You should keep in touch with your doctor regularly.
- During treatment with Prograf capsules, your doctor may order several tests (including blood, urine, heart function, visual and neurological tests) from time to time. This is a normal procedure and it will help your doctor to decide what is the most suitable dosage of Prograf for you.
- Avoid taking any herbal remedies, e.g., St. John's wort [*Hypericum perforatum*], or any other herbal products, as this may affect the effectiveness and the dose of Prograf that you need to receive. If in doubt, please consult your doctor prior to taking any herbal products or remedies.
- If you have liver problems or any disease that may affect your liver, inform your doctor as this may affect the dosage of Prograf you are receiving.
- If you feel strong abdominal pain accompanied or not by other symptoms, such as chills, fever, nausea or vomiting.
- If you have diarrhea for more than one day, please tell your doctor, because it might be necessary to adjust the dose of Prograf that you are receiving.
- If there is a change in the electrical conduction of your heart called "QT prolongation".
- Limit your exposure to sunlight and UV light while taking Prograf by wearing appropriate protective clothing and using a sunscreen with a high sun protection factor. The reason is the potential risk of malignant skin changes with immunosuppressive therapy.
- If you need to receive any vaccinations, inform your doctor beforehand. Your doctor will recommend to you the best method of treatment.
- Patients treated with Prograf have been reported to have an increased risk of lymphoproliferative disorders (see section 4 - "Side effects"). Consult the doctor regarding these disorders.
- If you have or have had damage to the smallest blood vessels, known as thrombotic microangiopathy/thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome. Tell your doctor if you develop fever, bruising under the skin (which may appear as red dots), unexplained tiredness, confusion, yellowing of the skin or eyes, reduced urine output, vision loss and seizures (see section 4 - "Side effects"). When tacrolimus is taken together with sirolimus or everolimus, the risk of developing these symptoms may increase.

Precaution for handling:

Direct contact with any part of your body like your skin or eyes, or breathing in of injection solutions, powder or granules contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and eyes.

Drug-drug interactions

If you are taking or have recently taken other medicines including non-prescription medicines and food supplements, tell the doctor or the pharmacist.

- Prograf should not be taken together with cyclosporin.

If you need to attend a doctor other than your transplant specialist, tell the doctor that you are taking tacrolimus. Your doctor may need to consult your transplant specialist if you should use another medicine that could increase or decrease your tacrolimus blood level.

Prograf blood levels can be affected by other medicines you take, and blood levels of other medicines can be affected by taking Prograf. This may require stopping treatment, or increasing or decreasing the Prograf dose. Some patients have experienced increases in tacrolimus blood levels while taking other medicines. This could lead to serious side effects, such as kidney problems, nervous system problems, and heart rhythm disturbances (see section 4).

An effect on the Prograf blood levels may occur very soon after starting the use of another medicine, therefore frequent continued monitoring of your Prograf blood level may be needed within the first few days of starting another medicine and frequently while treatment with the other medicine continues. Some other medicines may cause tacrolimus blood levels to decrease, which could increase the risk of rejecting the transplanted organ. In particular, you should tell your doctor if you are taking or have recently taken medicines with active ingredients such as:

- Antifungals and antibiotics, especially macrolide antibiotics, which are used for treatment of infections, such as ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole, clotrimazole, isavuconazole, miconazole, caspofungin, telithromycin, erythromycin, clarithromycin, josamycin, azithromycin, rifampicin, rifabutin, isoniazid and flucloxacillin.
- Letermovir, which is used to prevent an illness caused by the human cytomegalovirus (CMV).
- HIV-protease inhibitors (e.g. ritonavir, nelfinavir and saquinavir), the enhancer cobicistat and combined tablets or HIV non-nucleoside reverse transcriptase inhibitors (efavirenz, etravirine, nevirapine), which are used for treatment of HIV infection (human immunodeficiency virus).
- HCV protease inhibitors (e.g. telaprevir, boceprevir, the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir), which are used for treatment of hepatitis C infection.
- Nilotinib and imatinib, idelalisib, ceritinib, crizotinib, apalutamide, enzalutamide, or mitotane (used for treatment of certain cancer types).
- Mycophenolic acid which is used for immunosuppression for prevention of graft rejection.
- Medicines to treat gastric ulcer and acid reflux (e.g., omeprazole, lansoprazole or cimetidine).
- Medicines to treat nausea and vomiting (e.g. metoclopramide).
- Antacids that contain magnesium-aluminum-hydroxide for treatment of heartburn.
- Hormonal treatments that contain ethinylestradiol (e.g. contraceptive tablets) or danazol.
- Antihypertensives and medicines for heart problems, e.g. nifedipine, nicardipine, diltiazem, verapamil.
- Anti-arrhythmics (e.g. amiodarone) which are used for treatment of heartbeat disturbances (arrhythmia).
- Medicines called statins which are used for treatment of high levels of cholesterol and triglycerides.
- The anti-epileptics carbamazepine, phenytoin or phenobarbital.
- Metamizole, used to treat pain and fever.
- The corticosteroids prednisolone and methylprednisolone.
- The antidepressant nefazodone.
- Herbal medicines that contain Hypericum (St. John's wort [*Hypericum perforatum*]) or *Schisandra sphenanthera* extracts.
- Cannabidiol (uses amongst others include treatment of seizures).

Tell your doctor if you are receiving treatment for hepatitis C. The drug treatment for hepatitis C may change your liver function and may affect blood levels of tacrolimus. Tacrolimus blood levels may fall or may

increase depending on the medicines prescribed for hepatitis C. Your doctor may need to closely monitor tacrolimus blood levels and make necessary adjustments of Prograf dose after you start treatment for hepatitis C.
Inform the doctor if you are taking or should take ibuprofen, amphotericin B, antibiotics (cotrimoxazole, vancomycin, or so-called aminoglycoside antibiotics such as gentamicin), or antiviral medicines (e.g. acyclovir, ganciclovir, cidofovir, or foscarnet). These medicines may worsen kidney or nervous system problems when taken together with Prograf.
Tell your doctor if you are taking sirolimus or everolimus. When tacrolimus is taken together with sirolimus or everolimus, the risk of developing thrombotic microangiopathy, thrombotic thrombocytopenic purpura, and haemolytic uraemic syndrome may increase (see section 4- "Side effects").
In addition, tell your doctor if you are taking potassium supplements or potassium-sparing diuretics (e.g. amiloride, triamterene or spironolactone), or the antibiotics trimethoprim or cotrimoxazole that may increase levels of potassium in your blood, non-steroidal anti-inflammatory drugs (NSAIDs, e.g. ibuprofen), used for fever, inflammation and pain anticoagulants (blood thinners), or oral antidiabetics, while taking Prograf.
If you need to receive any vaccinations, inform your doctor beforehand.

Use of the medicine and food
You should generally take the medicine on an empty stomach or at least 1 hour before or 2-3 hours after a meal. Grapefruit and grapefruit juice should be avoided while taking Prograf.

Pregnancy and breastfeeding
If you are pregnant or breastfeeding, thinking you might be pregnant or are planning to become pregnant, consult a doctor or a pharmacist before taking this medicine.
Prograf is excreted into breastmilk. Therefore, you should not breastfeed while taking Prograf.

Driving and operating machinery
Do not drive, use tools or operate machinery if you are feeling dizziness or sleepiness, or if you cannot see clearly after taking Prograf. These effects are more frequently observed if Prograf is taken in conjunction with alcohol use.

Important information about some ingredients of the medicine
Prograf capsules contain lactose. If you have been told by your doctor that you have an intolerance to certain sugars, speak to your doctor before taking this medicine.
The printing ink used on Prograf 0.5 mg and 1 mg capsules contains soya lecithin. If you are sensitive to peanuts or soya, inform the doctor in order to determine if you should take this medicine.
This medicine contains less than 23 mg of sodium in a capsule and is therefore considered sodium-free.

3. How should you use the medicine?

Always use the preparation according to the doctor's instructions.
Check with the doctor or pharmacist if you are uncertain about the dosage and how to use the preparation.
You should make sure that you are receiving the same tacrolimus preparation every time you get the medicine at the pharmacy, unless the specialist from the transplant clinic you are treated in has agreed to change to another tacrolimus preparation.
The dosage and treatment regimen will be determined only by the doctor.
The generally accepted dosage is:
This medicine should be taken twice a day. If you notice any change in the appearance of this medicine or in the instructions of use, inform your doctor or pharmacist as soon as possible to make sure that you are taking the right medicine.
The starting dose to prevent the rejection of your transplanted organ will be determined by your doctor and calculated according to your body weight. Initial doses just after transplantation will generally be in the range of 0.075-0.30 mg per kg body weight per day, depending on the transplanted organ.
The appropriate dosage for you depends on your general condition and on which other immunosuppressive medications you are taking.
Regular blood tests as ordered by your doctor will be required to determine the correct dose and to adjust it from time to time. Your doctor will consider reducing your Prograf dosage once your condition has stabilized. Your doctor will tell you exactly how many capsules to take and how often.
Do not exceed the recommended dose.

Method of use
Prograf should be taken orally twice daily, usually in the morning and evening. Prograf should generally be taken on an empty stomach or at least 1 hour before or 2-3 hours after a meal. The capsules should be swallowed whole with a glass of water. Take the capsules immediately following removal from the blister. Avoid grapefruit and grapefruit juice while taking Prograf. Do not swallow the desiccant contained in the aluminum wrapping.

If you accidentally took an overdose
If you accidentally took an overdose of this medicine or if a child accidentally swallowed this medicine, refer to your doctor or a hospital emergency room immediately and bring the package of the medicine with you.

If you have forgotten to take the medicine
Do not take a double dose in order to compensate for the dose that you forgot to take.
If you have forgotten to take a Prograf capsule, wait until it is time for the next dose and continue to take the capsules as usual.
Follow the treatment as recommended by the doctor.

If you stop taking the medicine
Stopping treatment with Prograf may increase the risk of rejection of your transplanted organ. Do not stop your treatment unless your doctor tells you to do so.

Do not take medicines in the dark! Check the label and the dose <u>every time</u> you take the medicine. Wear glasses if you need them.
If you have any other questions regarding use of the medicine, consult the doctor or the pharmacist.

4. Side effects

As with any medicine, using Prograf may cause side effects in some users. Do not be alarmed when reading the list of side effects. You may not experience any of them.
Prograf reduces your body's own defense mechanism (immune system), which will not be as good at fighting infections. Therefore, you may be more prone to infections while you are taking Prograf.
Some infections could be serious or fatal and may include infections caused by bacteria, viruses, fungi, parasites, or other infections.
Tell your doctor immediately if you get signs of an infection including:
- Fever, cough, sore throat, feeling weak or generally unwell.
- Memory loss, trouble thinking, difficulty walking or loss of vision - these may be due to a very rare, serious brain infection, which can be fatal (Progressive Multifocal Leukoencephalopathy or PML).

Severe side effects may occur, including the ones listed below.
Refer to the doctor immediately if you experience or suspect you may be experiencing any of the following severe side effects:
Serious common side effects (may affect up to 1 in 10 people):
- Gastrointestinal perforation: strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting.
- Insufficient function of your transplanted organ.
- Blurred vision.

Serious uncommon side effects (may affect up to 1 in 100 people):
- Thrombotic microangiopathy (damage to the smallest blood vessels) including haemolytic uraemic syndrome, a condition with the following symptoms: low or no urine output (acute renal failure), extreme tiredness, yellowing of the skin or eyes (jaundice) and abnormal bruising or bleeding and signs of infection.

Serious rare side effects (may affect up to 1 in 1,000 people):
- Thrombotic Thrombocytopenic Purpura: a condition involving damage to the smallest blood vessels and characterised by fever and bruising under the skin that may appear as red pinpoint dots, with or without unexplained extreme tiredness, confusion, yellowing of the skin or eyes (jaundice), with symptoms of acute renal failure (low or no urine output), vision loss and seizures.
- Toxic epidermal necrolysis: erosion and blistering of skin or mucous membranes, red swollen skin that can detach in large parts of the body.
- Blindness.

Serious very rare side effects (may affect up to 1 in 10,000 people):
- Stevens-Johnson syndrome: unexplained widespread skin pain, facial swelling, serious illness with blistering of skin, mouth, eyes and genitals, hives, tongue swelling, red or purple skin rash that spreads, skin shedding.
- *Torsades de pointes*: change in the heart frequency that can be accompanied or not of symptoms, such as chest pain (angina), faint, vertigo or nausea, palpitations (feeling the heartbeat) and difficulty breathing.

Serious side effects - frequency not known (frequency cannot be estimated from the available data):
• Opportunistic infections (bacterial, fungal, viral or parasite): prolonged diarrhea, fever and sore throat.

- Incidents of benign and malignant tumors resulting from immunosuppressive therapy have been reported.
- Cases of pure red blood cell aplasia (a sharp decline in red blood cell counts), hemolytic anemia (a decline in red blood cell counts as a result of abnormal breakdown of these cells accompanied by tiredness) and febrile neutropenia (a decline in the type of white blood cells that fight infection, accompanied by fever). It is not known exactly how often these side effects occur. You may not experience any symptoms at all, or depending on the severity of your condition, you may experience: fatigue, apathy, abnormal paleness of the skin, shortness of breath, dizziness, headaches, chest pains and cold sensation in the hands and feet.
- Cases of agranulocytosis (a sharp decline in white blood cell counts, accompanied by mouth sores, fever and infections). You may not have any symptoms at all, or you may have a sudden fever, chills and sore throat.
- Allergic and anaphylactic reactions, manifested by the following symptoms: a sudden itchy rash (hives), swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and you may feel on the verge of fainting.
- Posterior Reversible Encephalopathy Syndrome (PRES): headache, confusion, mood changes, fits, and disturbances of your vision. These could be signs of a disorder known as posterior reversible encephalopathy syndrome, which has been reported in some patients treated with tacrolimus.
- Optic neuropathy (abnormality of the optic nerve): problems with your vision such as blurred vision, changes in colour vision, difficulty in seeing detail or restriction of your field of vision.

The following side effects may also occur after taking Prograf and could be serious:

Very common side effects (may affect more than 1 in 10 patients):
- Increased blood sugar, diabetes mellitus, increased potassium in the blood
- Sleeping difficulties
- Tremor, headache
- Rise in blood pressure
- Liver function tests abnormal
- Diarrhea, nausea
- Kidney problems

Common side effects (may affect up to 1 in 10 patients):
- Reduction in blood cell counts (platelets, red or white blood cells), increase in white blood cell counts, changes in red blood cell counts (seen in blood tests)
- Reduced magnesium, phosphate, potassium, calcium or sodium in the blood, fluid overload, increased level of uric acid or lipids in the blood, decreased appetite, increased acidity of the blood, other changes in blood salts
- Anxiety symptoms, confusion and disorientation, depression, mood changes, nightmares, hallucinations, mental disorders
- Convulsions, disturbances in consciousness, tingling and numbness (sometimes painful) in the hands and feet, dizziness, impaired writing ability, nervous system disorders
- Increased sensitivity to light, eye disorders
- Tinnitus (ringing sound in your ears)
- Reduced blood flow in blood vessels in the heart, rapid heartbeat
- Bleeding, partial or complete blocking of blood vessels, reduced blood pressure
- Shortness of breath, changes in lung tissue, collection of fluids around the lungs, inflammation of the pharynx, cough, flu-like symptoms
- Inflammations or ulcers causing abdominal pain or diarrhea, bleeding in the stomach, inflammations or ulcers in the mouth, collection of fluids in the abdomen, vomiting, abdominal pains, indigestion, constipation, flatulence, bloating, loose stools, stomach problems
- Changes in liver enzymes and function, yellowing of the skin due to liver problems, liver tissue damage and inflammation of the liver
- Itching, rash, hair loss, acne, increased sweating
- Pain in joints, limbs, back and feet, muscle cramps
- Renal failure, reduced production of urine, impaired or painful urination
- General weakness, fever, collection of fluids in your body, pain and discomfort, increase in the levels of the enzyme alkaline phosphatase in your blood, weight gain, sensation of changes in body temperature

Uncommon side effects (may affect up to 1 in 100 patients):
- Changes in blood clotting, reduction in all blood cell counts
- Dehydration
- Reduced protein or sugar levels in the blood, increased phosphate levels in the blood
- Coma, bleeding in the brain, stroke, paralysis, brain disorder, speech and language impairments, memory problems
- Blurry vision due to impairment of the eye lens
- Impaired hearing
- Irregular heartbeat, cardiac arrest, reduced heart performance, impaired heart muscle, enlargement of the heart muscle (hypertrophic cardiomyopathy), stronger heartbeat, abnormal ECG, abnormal heart rate and pulse
- Blood clot in a vein of a limb, shock
- Breathing difficulties, respiratory tract disorders, asthma
- Obstruction of the gut, increase in the levels of the enzyme amylase in your blood, reflux of stomach content into the throat, delayed emptying of the stomach
- Dermatitis, burning sensation in sunlight
- Joint disorders
- Inability to urinate, painful menstruation and abnormal menstrual bleeding
- Failure of some organs, flu-like illness, increased sensitivity to heat and cold, sensation of pressure in your chest, agitation or abnormal feeling, increase in the levels of the enzyme lactate dehydrogenase in your blood, weight loss

Rare side effects (may affect up to 1 in 1,000 patients):
- Small bleedings in your skin due to blood clots
- Increased muscle stiffness
- Deafness
- Collection of fluids around the heart
- Acute shortness of breath
- Cyst formation in your pancreas
- Problems with blood flow in the liver
- Excessive hairiness
- Thirst, tendency to fall, feeling of tightness in your chest, decreased mobility, ulcer

Very rare side effects (may affect up to 1 in 10,000 patients):
- Muscle weakness
- Abnormal results in echocardiogram
- Liver failure, narrowing of the bile vessel
- Painful urination with blood in the urine
- Increase in fat tissue

If a side effect occurs, if one of the side effects worsens, or if you suffer from a side effect not mentioned in this leaflet, consult your doctor.

Reporting side effects
Side effects may be reported to the Ministry of Health by clicking on the link “report side effects due to medicinal treatment” found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following link:
https://sideeffects.health.gov.il

5. How to store the medicine?
Avoid poisoning! This medicine and any other medicine must be kept in a closed place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.
Take the capsules immediately following removal from the blister.
Store below 25°C. Keep in original package to protect from moisture.
After opening the aluminum wrapping the capsules should be used within 12 months, but no later than the expiry date indicated on the package.
In each aluminum wrapping there is a desiccant (moisture absorber).
Do not swallow.

6. Additional information

In addition to the active ingredient, the medicine also contains:

Prograf capsules 0.5 mg

Capsule content composition:
Lactose monohydrate, magnesium stearate, hydroxypropyl methylcellulose, croscarmellose sodium

Capsule shell composition:
Titanium dioxide (E 171), ferric oxide yellow (E 172), gelatin, shellac glaze, lecithin (soya), simeticone, ferric oxide red (E 172), hydroxypropyl cellulose

Prograf capsules 1 mg

Capsule content composition:
Lactose monohydrate, hydroxypropyl methylcellulose, croscarmellose sodium, magnesium stearate

Capsule shell composition:
Titanium dioxide (E 171), gelatin, shellac glaze, lecithin (soya), simeticone, ferric oxide red (E 172), hydroxypropyl cellulose

Prograf capsules 5 mg

Capsule content composition:
Lactose monohydrate, hydroxypropyl methylcellulose, croscarmellose sodium, magnesium stearate

Capsule shell composition:
Titanium dioxide (E 171), ferric oxide red (E 172), gelatin, shellac, propylene glycol

What does the medicine look like and what are the contents of the package

Prograf capsules 0.5 mg
Light yellow capsules imprinted in red with “0.5 mg” and “[f] 607”, containing white powder

Prograf capsules 1 mg
Opaque white capsules imprinted in red with “1 mg” and “[f] 617”, containing white powder

Prograf capsules 5 mg
Opaque greyish-red capsules imprinted in white with “5 mg” and “[f] 657”, containing white powder

The package contains 50 or 100 capsules, packed in trays (blisters), in an aluminum wrapping that contains a desiccant.
Not all package sizes may be marketed.

License holder and the address:
Astellas Pharma International B.V., 21 Hamelacha St., Rosh Ha’ayin, 4809157, Israel

Name and address of the manufacturer:
Astellas Ireland Co. Ltd., Killorglin, Ireland

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Revised in 11.2022 according to MoH guidelines

Registration numbers of the medicine in the National Drug Registry of the Ministry of Health:

Prograf 0.5 mg:	122.07.30215
Prograf 1 mg:	107.69.29158
Prograf 5 mg:	107.70.29159